
Improved Computational Identification of Drug Response Using Optical Measurements of Human Stem Cell Derived Cardiomyocytes in Microphysiological Systems.

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Public Summary:

In this paper we have developed improved methodology to identify drug induced changes more efficiently, and quantitate important metrics such as drug-induced toxicity in line with published values. Consequently, the novel methodology is a step towards employing computational procedures to elucidate drug effects in adult cardiac tissue, potentially providing safer drugs to patients.

Scientific Abstract:

Cardiomyocytes derived from human induced pluripotent stem cells (hiPSC-CMs) hold great potential for drug screening applications. However, their usefulness is limited by the relative immaturity of the cells' electrophysiological properties as compared to native cardiomyocytes in the adult human heart. In this work, we extend and improve on methodology to address this limitation, building on previously introduced computational procedures which predict drug effects for adult cells based on changes in optical measurements of action potentials and Ca(2+) transients made in stem cell derived cardiac microtissues. This methodology quantifies ion channel changes through the inversion of data into a mathematical model, and maps this response to an adult phenotype through the assumption of functional invariance of fundamental intracellular and membrane channels during maturation. Here, we utilize an updated action potential model to represent both hiPSC-CMs and adult cardiomyocytes, apply an IC50-based model of dose-dependent drug effects, and introduce a continuation-based optimization algorithm for analysis of dose escalation measurements using five drugs with known effects. The improved methodology can identify drug induced changes more efficiently, and quantitate important metrics such as IC50 in line with published values. Consequently, the updated methodology is a step towards employing computational procedures to elucidate drug effects in adult cardiomyocytes for new drugs using stem cell-derived experimental tissues.

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